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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,453	10/25/1999	PETER FRANCIS LEADLAY		8705

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EXAMINER
KERR, KATHLEEN M

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1652	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

B-5

Office Action Summary	Application No.	Applicant(s)	
	09/214,453	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

KK 8/19/03

4)☒ Claim(s) *1-3,24-27,29,31-37,39 and 44-~~59~~ 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,24-27,29,31-37,39 and 44-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action (Paper No. 16 mailed September 11, 2001), Applicants filed a response and amendment (Paper No. 17 received March 21, 2002). Said amendment amended the specification and Claims 24, 27, 29, 31-34, and 37-39. Said amendment also cancelled Claims 28, 30, 38, and 40-43 and added new Claims 44-58. Thus, Claims 1-3, 24-27, 29, 31-37, 39, and 44-58 are pending in the instant application and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the International Application No. PCT/GB97/01819 filed on July 4, 1997 which claims benefit of (1) U.S. Provisional Application No. 60/024,188 filed on August 19, 1996, (2) Great Britain foreign application 9614189.0 filed on July 5, 1996, and (3) Great Britain foreign application 971062.3 filed on May 28, 1997 as requested in the declaration.

Drawings

3. As previously noted, the drawings are considered informal for the reasons detailed in the PTO Form 948 attached to the previous Office action (Paper No. 16). Appropriate correction is required prior to allowance.

Compliance with the Sequence Rules

4. By virtue of Applicant's amendment to the specification citing SEQ ID NOs, the instant application is now in compliance with the sequence rules.

Withdrawn - Objections to the Specification

5. Previous objection to the specification for lacking continuity data in the first paragraph is withdrawn by virtue of Applicants' amendment to the specification.

6. Previous objection to the specification for not containing an abstract is withdrawn by virtue of Applicants' amendment adding an Abstract.

7. Previous objection to the title for not completely describing the claimed subject matter is withdrawn by virtue of Applicant's amendment to the title.

8. Previous objection to the specification for lacking a section labeled "Brief Description of the Drawings" is withdrawn by virtue of Applicant's amendment to the specification.

Withdrawn - Claim Objections

9. Previous objection to Claim 3 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn. Applicants have explained that not all loading domains contain AT and ACP domains; in particular, the rapamycin loading domain contains only an adenylation and a reductase domain. Thus, this objection is withdrawn since Claim 3, as written, now further limits the subject matter of the parent claim.

10. Previous objection to Claim 24 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' amendment and explanation of the instant claim. However, the Examiner

notes that Claim 24 is drawn to a hybrid PKS gene that, for example, minimally is AT_L-ACP_L-KS_L-AT_X-ACP_X-KS_Y-AT_Y-ACP_Y. Since the first KS of the gene as shown must be homologous to the loading AT-ACP, the first extending AT-ACP ("X") is not a complete extension module as a heterologous entity. Thus, the "Y" extension module is required to meet the limitation of the claims wherein an extension module is heterologous; "Y" can be equal to "X" in the example above. This is required because the heterologous extension module must be a complete (KS-AT-ACP) extension module. This adds limitations on the claim that do not appear to be appreciated by Applicants. The Examiner reiterates the suggestion of making Claim 24 independent to claim the scope intended by Applicants as described in the response (Paper No. 17).

Withdrawn - Claim Rejections - 35 U.S.C. § 112

11. Previous rejection of Claim 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for being wholly confusing is withdrawn by virtue of Applicants' amendment. However, a new rejection is set forth below based on the implications of the new claim and how these implications are not aligned with the actual claim limitations.

12. Previous rejection of Claim 27 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "an avr loading module" is withdrawn by virtue of Applicants' amendment which replaces the abbreviation with a clear description of the term.

13. Previous rejection of Claim 28 under 35 U.S.C. § 112, second paragraph, as being indefinite for being wholly unclear is withdrawn by virtue of Applicants' cancellation of said claim. Applicants present case law concerning 35 U.S.C. § 112, second paragraph, and Claim 28

(see page 34 of Applicants' response, Paper No. 17). Applicants argue that the term "combinatorial module" is defined on page 9 and/or page 2 of the specification; the Examiner disagrees. These definitions are wholly unclear as to the metes and bounds of the term. Moreover, Applicants' argue the "nature of (extension) modules which are no where in the original Claim 28. The Examiner maintains the position of Claim 28 being wholly unclear. However, this rejection is moot, as noted above, because Applicants' have cancelled the instant claim. From Applicants' arguments, it would seem that Applicants are under the impression that Claim 28 is still pending; this is not the case since Claim 28 is cancelled on page 26 of Applicants' response.

14. Previous rejection of Claims 29 and 31-34 under 35 U.S.C. § 112, second paragraph, as being indefinite for the words "nucleic acid" is withdrawn by virtue of Applicants' amendment.

15. Previous rejection of Claim 30 under 35 U.S.C. § 112, second paragraph, as being indefinite for being wholly unclear is withdrawn by virtue of Applicants' cancellation of said claim.

16. Previous rejection of Claims 32 and 34 under 35 U.S.C. § 112, second paragraph, as being indefinite for the claim limitation of having a "natural activator gene" is withdrawn by virtue of Applicant's amendment.

17. Previous rejection of Claim 38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrases "'donor' DNA" and "heterologous chromosomal PKS DNA" is withdrawn by virtue of Applicants' cancellation of said claim.

18. Previous rejection of Claims 37 and 39 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112

19. Previous rejection of Claim 29 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that a reference to the rapamycin gene cluster in Schwecke *et al.* coupled with a remark elsewhere in the specification concerning an unusual chain terminating domain of the rapamycin gene cluster meets the criteria for written description of this concept in the instant claim. The Examiner disagrees. As previously noted, to satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. This species (the rapamycin terminating domain) of the claimed genus that Applicants argue has been adequately described is wholly lacking a description of the structure. The reference to Schwecke *et al.* is inadequate to describe the structure unless Schwecke *et al.* is expressly incorporated by reference. In the event that the structure of the rapamycin gene cluster has been expressly incorporated into the specification by reference, such a disclosure of a single species of the claimed genus would not adequately describe the genus because one of skill in the art would be unable to predictably define the structure of other members of the genus without some description of a correlation between the structure and claimed function.

20. The previous rejection of Claim 29 has been altered as follows. Since the same reasoning for the rejection applies and Applicants have traversed said reasoning, the rejection is considered to be maintained in part.

Claim 29 stands rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for hybrid PKS genes containing the rapamycin chain terminating domain, does not reasonably provide enablement for hybrid PKS genes containing other chain terminating domains other than TE domains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Chain terminating thioesterase (TE) domains in PKS genes are well known in the art as the enzymes which cleave the developed polyketide from the enzymes which produced it along the PKS enzyme complex. Only a single example of an enzyme catalyzing such an activity is identified in the art as part of the rapamycin gene cluster. Applicants' have presented no guidance or working examples for the identification of other such a nucleic acid sequences. Thus, the identification and use of such a product, with the exception of the rapamycin chain-terminating domain, is wholly unpredictable.

21. Previous rejection of Claim 39 under 35 U.S.C. § 112, first paragraph, scope of enablement, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the prior art (Roberts *et al.* (1993) and Leadlay *et al.* (1993)) teaches proper folding and assembly of PKS proteins. While the Examiner agrees, the instant claims are drawn to methods of making polyketides in microorganisms and Roberts *et al.* and Leadlay *et al.* make polyketides in transformed host cells. The *only* disclosure in the prior

art and in the instant specification at the time of the invention is the production of polyketides using transformed host cells wherein the host cells natively produce polyketides using endogenous PKS enzymes. All the noted references in Applicants' arguments, alone or in combination, do not produce polyketides in a transformed host cell wherein the host cells natively produce polyketides using endogenous PKS enzymes. This fact is not disputed by Applicants and is the basis of the rejection. The ability to produce polyketides in any transformed host cell would require unpredictable experimentation. Applicants present no guidance of direction for the purpose of using other organisms. The state of the prior art is such that using other organisms is wrought with difficulties and wholly unpredictable. Thus, the instant claim is not enabled to the full extent of its scope by virtue of the specification or the prior art at the time of the invention.

For all of the above reasons, the instant rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 102

22. Previous rejection of Claims 1, 31-37, and 39 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290 effective filing date of June 7, 1995 via divisional parent USPN 5,712,146) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants present extensive arguments (pages 40-43 of the response) concerning the support of the claims cited in the instant rejection back to the original filing date of Khosla *et al.* (June 7, 1995). This filing date is based on the divisional filing of USPN 5,962,290, divided from USPN 5,712,146. No new matter can be added to an application as a continuation or a division of a parent application; therefore, based on the full faith and credit given to patented

U.S. applications, the support for **all** the claims patented in USPN 5,962,290 and noted in the previous rejection is, without question, granted the earliest effective filing date of June 7, 1995. Applicants cite *In re* Benno concerning the difference between claims and a specification. However, the comments in this case are related to infringement. Applicants proceed to argue that Khosla *et al.* (USPN 5,962,290) contains new matter relative to the earliest effective filing date of June 7, 1995 ("The description in the Khosla patent is almost the same as in the application as filed" and "The additions and alterations made after the present applicants's filing and publication dates added new concepts to the application that were not originally present." see response page 42). In the examination of the instant application, the Examiner is not permitted to assess the validity (particularly with respect to the addition of any new matter during the prosecution) of issued U.S. patents; all issued U.S. patents are considered valid as issued. Thus, all arguments relating to the support of the issued claims in the specification as originally filed on June 7, 1995 are not persuasive.

Applicants argue that Khosla *et al.* do not enable the disclosure of hybrid clusters that include type I and type II PKSs; Applicants provide no arguments supporting this statement. The Examiner disagrees with this statement. Khosla *et al.*, in combination with the state of the art at the time of their invention (at least June 7, 1995), have enabled the construction and use of hybrid PKS gene clusters since these are merely recombinant gene products.

Applicants continue to argue that claims in USPN 5,962,290, as based on the filing date of the divisional parent USPN 5,712,146 filed on June 7, 1995, are not prior art. As previously stated, the entirety of USPN 5,962,290 is granted an effective filing date of June 7, 1995; and said claims are prior art.

Applicants argue that "statements of Khosla *et al.* from publications dating from after Khosla *et al.* '146 and '290 provide some guidance as to how much genuine disclosure they contain." (see page 47 of response). Again, this argument strives to alter the effective filing date of USPN 5,962,290; any arguments to this fact are not persuasive for the reasons noted above. To overcome the instant rejection, Applicants must demonstrate that USPN 5,962,290, as patented with an effective filing date of June 7, 1995, does not teach the claimed invention. No such arguments are presented.

Maintained - Claim Rejections - 35 U.S.C. § 103

23. Previous rejection of Claims 2, 3, 25, and 26 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that Khosla *et al.* do not "particularly teach" all domain combinations as noted by the Examiner. The Examiner disagrees; the point is maintained that Khosla *et al.* do teach all domain combinations. Moreover, the specific combinations in the instant claims are obvious for the reasons previously cited.

Applicants argue that Khosla *et al.* is not an enabling disclosure of the claims products. The Examiner disagrees with this statement. Khosla *et al.*, in combination with the state of the art at the time of their invention (at least June 7, 1995), have enabled the construction and use of hybrid PKS gene clusters since these are merely recombinant gene products.

24. Previous rejection of Claim 27 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of Kao *et al.* is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that Khosla *et al.* do not disclose type I/type I hybrids; this rejection is based on the new matter concept presented and rebutted in the 102 rejection above.

Applicants argue that Khosla *et al.* is not an enabling disclosure of the claims products. The Examiner disagrees with this statement. Khosla *et al.*, in combination with the state of the art at the time of their invention (at least June 7, 1995), have enabled the construction and use of hybrid PKS gene clusters since these are merely recombinant gene products.

NEW REJECTIONS

Objections to the Specification

25. In the amendment filed March 21, 2002, to page 63, line 7, there appears to be a typographical error in which lines have been duplicated. Appropriate amendment to this paragraph is required.

26. The amendment filed March 21, 2002 (Paper No. 17) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Claims 45, 46, and 52. In Claim 45, language such as "naturally contiguous", "downstream", and first-sixth modules does not have clear support; Applicants have not cited support for this new claim. In Claim 46, language

such as "first ketide unit" and "adapted to contribute" does not have clear support. Applicants cite original Claim 30 as support, but the language in Claim 46 is much more expansive. In Claim 52, language such as "mutually adapted" does not have clear support. Applicants cite page 9 and page 16, but clear support for Claim 52 is lacking on these pages.

Applicant is required to cancel the new matter or cite clear support (page and line number) in the specification as originally filed in the reply to this Office Action.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Previously, an objection was made against the instant claim noting the lack of further limiting nature of the claim, and a rejection was made against the instant claim because of its apparent dual requirement wherein the KS portion was required to be heterologous (as required by the limitations of Claim 1) and homologous (as required by the limitations of Claim 24) at the same time. While the Examiner can interpret the claim in view of its parent claims, this interpretation does not appear to be the scope of the claim intended by Applicants as based on their arguments in Paper No. 17.

The Examiner notes that Claim 24 must encompass all the limitations of Claims 1 and 2 from which it depends. From Claim 1, the first domain-containing portion and the second domain-containing portion must be heterologous. From Claim 2, the first portion must contain at

least a loading module, and the second portion must contain at least an extender module. Thus, Claim 24 is drawn to a hybrid PKS gene that, for example, minimally contains:

AT_L-ACP_L-KS_L-AT_X-ACP_X-KS_Y-AT_Y-ACP_Y (i.e., two extender modules).

Since only the first KS of the gene, as shown, can be homologous to the loading AT-ACP, the first extending AT-ACP ("X" above) is not a complete extension module as a heterologous entity. Thus, the "Y" extension module is required to meet the limitation of the claims (wherein an extension module of the second portion is heterologous); "Y" can be equal to "X" in the example above. This second complete extension module is required because the heterologous extension module must be a complete (KS-AT-ACP) extension module. This adds limitations on the claim that do not appear to be appreciated by Applicants. Since these limitations are not appreciated by Applicants, they are apparently unclear as written. The Examiner reiterates the suggestion of making Claim 24 independent to claim the scope intended by Applicants as described in the response (Paper No. 17), which would be clear if appropriately amended, as containing:

AT_L-ACP_L-KS_L-AT_X-ACP_X- (i.e., at least one extender module).

28. Claim 45 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim is wholly and entirely confusing. The limitation of the phrase beginning with "whereof" is wholly unclear. The distinction between clauses and which clauses modify which other products is wholly unclear. The "first and second points" lack any sort of definition. The additional modules numbered third, fourth, fifth, and sixth are wholly unclear as

to their content and placement on the nucleic acid claimed. This jumble of first and second, points, modules, and correspondence is wholly confusing. Perhaps appropriate indentation would facilitate the understanding of what Applicants intend to claim.

29. Claim 46 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim is wholly and entirely confusing. The phrase "a portion which replaces a nucleic acid portion" is unclear. The meaning of "adapted to contribute" is also unclear. Moreover, the construction of the entire claim leaves one of skill in the art wholly confused as to the claimed subject matter. Perhaps appropriate indentation would facilitate the understanding of what Applicants intend to claim.

30. Claims 45, 46, and 52 are rejected under 35 U.S.C. § 112, first paragraph, written description, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. See objection to the specification above for the specifics of the new matter content.

31. Claims 50 and 53 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 50 is drawn to a plasmid containing "an int sequence"; Claim 53 is drawn to methods using such a sequence.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The DNA in the plasmid of Claim 50 is claimed by its function – having the ability to integrate into a host's chromosome – not by its structure. One of skill in the art would be unable to identify the structures of other members of this claimed genus would some claim limitation relating to structure or some other descriptive limitation of structure in addition to function.

32. Claim 54 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 54 is drawn to a gene comprising a portion of the rapamycin gene cluster described functionally, not structurally.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The gene of Claim 54 is claimed by its function – having the ability to effect connection of the polyketide chain to an amino acid – not by its structure. One of skill in the art would be unable to identify the structures of other members of this claimed genus would some claim limitation relating to structure or some other descriptive limitation of structure in addition to function.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

> has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

33. Claims 47-49 and 55-58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290 effective filing date of June 7, 1995 via divisional parent USPN 5,712,146). The instant claims are drawn to plasmids and host cells containing nucleic acid sequences encoding hybrid modular PKS genes.

Khosla *et al.* teach a "DNA molecule which comprises a recombinant expression system for production of a hybrid modular (Type I) PKS...wherein said activities [KS, AT, ACP, etc.] are derived from at least two different modular PKS" (see Claim 10). Khosla *et al.* teach examples of genes for use in hybrid modular PKS clusters such as erythromycin, tylosin, carbomycin, spiramycin, avermectin, and candicidin (see column 14, lines 26-35). Khosla *et al.* further teach said DNA molecule operably linked to an actinorhodin (act) promoter (see Claim 17) in the presence of "actII-ORF4, an activator gene, which is required for transcription from these [actI/actIII] promoters" (see column 19, lines 38-40). Khosla *et al.* further teach host cells containing said DNAs (see Claims 11 and 18), the production of which host cells inherently require the use of vectors. Khosla *et al.* also teach methods of making modular PKSs as encoded by said DNA molecules (see Claims 12 and 19), the product of which methods is the claimed hybrid PKS enzymes of Applicants' Claim 35. Said methods of making modular PKSs are inherently also methods of making polyketides, as claimed in Applicants' Claim 39. Moreover, Khosla *et al.* teach that their methods are useful for "efficiently producing both new and known polyketides, using recombinant technology" (see column 3, lines 7-10). Lastly, Khosla *et al.* is replete with teachings of hybrid, (type I) modular PKS genes and enzymes (see for example,

column 4, lines 44-65, column 9, lines 38-50, column 13, lines 53-58, and column 25, lines 24-40).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

34. Claim 44 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (this rejection is identical to the rejection of Claim 3 since Claim 44 is equivalent to Claim 3 – see double patenting warning below). The instant claims are drawn to nucleic acid sequences encoding hybrid modular PKS genes wherein (1) said nucleic acid sequences include at least a loading domain and an extender domain, (2) said loading and extender domains are heterologous, (3) said loading domain initiates polyketide synthesis with a starter unit different from a starter unit normally utilized by said extender domain, and (4) said loading domain is capable of using many different starter units.

Khosla *et al.* teach as describe above. Khosla *et al.* further teach that the DEBS loading domain can use a multiplicity of starter units (see column 42, lines 39-41). Khosla *et al.* do not specifically teach an embodiment of a hybrid PKS gene that is the DEBS PKS gene cluster, a cluster which has a loading domain using more than one starter unit, with a substituted, corresponding domain from, for example, the modular PKS gene cluster for spiramycin. Such a PKS gene meets all the limitations of the instant claims.

It would have been obvious to one of ordinary skill in the art to produce the claimed invention because Khosla *et al.* particularly teach all domain combinations for hybrid PKS gene clusters using the noted modular PKS genes. One would have been motivated to produce such a hybrid PKS gene, specifically using the DEBS loading module, in view of the teachings of Khosla *et al.* concerning the relaxed specificity of the DEBS loader particularly since a more relaxed specificity can give rise to a greater variety of polyketides produce – the utility of the entire Khosla *et al.* disclosure.

35. Claim 51 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of Cox *et al.* (USPN 5,190,871). The instant claim is drawn to methods using nucleic acid sequences encoding hybrid modular PKS genes in host cells wherein said nucleic acid sequence are integrated into the host cell's chromosome.

Khosla *et al.* teach as describe previously. While Khosla *et al.* teach transforming host cells with hybrid PKS genes so that said genes are retained by the host cell, Khosla *et al.* do not teach said transformation by means of integrating into the host cell's chromosome.

Cox *et al.* teach stable integration of foreign DNA into host cell's chromosomes (see column 1, lines 25-35).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Khosla *et al.* and Cox *et al.* to produce the claimed invention because the teachings of Khosla *et al.* involve host cell transformation with antibiotic selection pressure. Gene integration is a commonly used mechanism for stable transformation. Albeit a more difficult method, said method offers more stable integration of the desired gene(s). One would have been motivated to produce the specific embodiment for more stable production of possible therapeutics as taught by

Khosla *et al.* Moreover, one would have had a reasonable expectation of success that the stable integrations would function together in view of the teachings of Khosla *et al.* and because the combination of modular PKS genes in a hybrid PKS has been shown to produce functional PKSs.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. § 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. § 101.

36. Applicant is advised that should claim 3 be found allowable, claim 44 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k).

37. Applicant is advised that should claim 35 be found allowable, claim 47 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other

as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). The difference between a vector and a plasmid is unclear from the art and/or the instant specification. Such a different would be the only means for distinguishing Claims 35 and 47 from each other.

Examiner Notes

38. Page 89 contains an embedded figure. Such figures are not permitted in the body of the specification and must be deleted and, if desired, added to the formal drawings of the application. See 37 C.F.R. § 1.58.

39. The Examiner notes a large gap on page 94 of the specification as originally filed. From the text, it seems as though a chemical formula is missing. Applicants are advised to consider this section of the specification for any missing components.

Conclusion

40. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
May 17, 2002